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We present here an interdisciplinary workshop on the subject of biomolecules offered to undergraduate and high-school students with the aim of boosting their interest toward all areas of science contributing to the study of life. The workshop involves Mathematics, Physics, Chemistry, Computer Science and Biology. Based on our own areas of research, molecular modeling is chosen as central axis as it involves all disciplines. In order to provide a strong biological motivation for the study of the dynamics of biomolecules, the theme of the workshop is the origin of life. All sessions are built around active pedagogies, including games, and a final poster presentation.

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Molecular modeling as the spark for active learning approaches for interdisciplinary biology teaching

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Abstract

We present here an interdisciplinary workshop on the subject of biomolecules offered to undergraduate and high-school students with the aim of boosting their interest toward all areas of science contributing to the study of life. The workshop involves Mathematics, Physics, Chemistry, Computer Science and Biology. Based on our own areas of research, molecular modeling is chosen as central axis as it involves all disciplines. In order to provide a strong biological motivation for the study of the dynamics of biomolecules, the theme of the workshop is the origin of life. All sessions are built around active pedagogies, including games, and a final poster presentation.

1. The route toward new teaching strategies

As natural sciences professors in life science departments, we are often confronted with the difficulties of our students with the perceived methodological rigor of the subjects we teach (mathematics, physics, chemistry) that seem to pose a much greater obstacle to the progression toward a degree than most other subjects. In our experiences we have identified at least two issues contributing to the disappointing results we often face. The first issue comes from the fact that students who choose life sciences might have done so precisely because they already have had difficulties with the related disciplines in previous years and therefore arrive at the college level with a shaky

background. The second issue comes from their difficulties in seeing the purpose of studying mathematics, physics and, to a lesser extent, chemistry, as a necessary and integral part of their curriculum. From our perspective the two issues are intertwined. We will not be successful in our teachings if we cannot clearly demonstrate the importance of our subjects to students and show them hands-on how concepts that might seem at first very abstract have a high practical use in biology. If we can get the students interested in our subjects, we then have the opportunity to address the first problem by reaching out to those who come to us with more difficulties from the start, and, by applying less conventional teaching methods, have the chance to help them fill the gaps in their knowledge.

Many previous experiences have taught us that traditional lectures do not constitute an appropriate and efficient solution to these issues, even when a lot of care is put into showing examples and applications from biology. The mere fact that our classes are named mathematics or physics may be enough to scare some students off. We then started experimenting different alternative solutions stemming also from our privileged position of researchers working at the interface between biological sciences, physics and chemistry. Inspired by active teaching methods [1], by our own personal experiences with the Montessori method [2], and after having had the chance to attempt different teaching strategies throughout the years, we developed a one week workshop, named RIGOLE (a French acronym for group work around the origins of life, and that in French corresponds to a word that could be translated as laughter) aimed at first and second year Life Science bachelor students. The goal of the workshop was, and still is, to boost students' interest and motivation by showing them through unconventional teaching how all subjects matter and how the knowledge from very different disciplines is needed to be able to tackle interesting and fundamental biological (research) questions. For this purpose, biomolecular modeling constitues an ideal playgound for bringing together the various disciplines around a common challenge. In order to break the barriers and the fears that students may have with respect to subjects such as chemistry, physics and mathematics, all teachings of the RIGOLE workshop are as much as possible interactive, integrating scientific games, hands-on activities, and group projects, together with short guiding lectures. Students have therefore the opportunity to see the importance of these disciplines in the context of a scientific challenge and to approach them from a new perspective and with less apprehension thanks to the active pedagogies.

2. Design of an interdisciplinary workshop

The workshop was developed in 2015 and ran several times since 2016. Overall, about 180 university students have participated. The workshop is since also offered to high school students, in an adapted version, with the aim of showing them early on in their curriculum the importance of each subject. This information gives them a first idea of the research carried out at university, and ultimately offers them the chance for a more educated choice of their future professional orientation. About 100 high school students have participated so far.

2.1. Setting goals

The workshop has two main objectives:

- Discover what is scientific research and understand the importance of interdisciplinarity through an itinerary around the questions of the origins of life from a molecular standpoint. Understand the interconnections between disciplines thanks to a global coherence of the workshop showing how each one is necessary to study the behavior of biomolecules through molecular dynamics simulation approaches.

- Motivate students for the study of scientific disciplines through an interactive and fun teaching where the student is the primary actor of the learning process.

More specifically, several sub-objectives have been identified to promote the effectiveness of the learning process.
Discover: the context of university research, different possible orientations after the second year of college, the pleasure of learning without pressure.
Understand: the coherence of first and second year life science curricula, concepts studied in first and second year courses, applying them to a specific problem, scientific reasoning, how different disciplines are interdependent.
Share: With students coming from different backgrounds and interests, with teachers coming from various scientific disciplines working side-by-side with the students, with more advanced university students helping in the course as tutors.
Enjoy: learning without fears, learning through games and practical activities, group work, open discussions with students and teachers.

2.2. The pedagogical and organisational approach

The workshop adopts a large variety of teaching methods including group activities, practical activities and on-line games and demos. Activities are always supervised and guided by professors and researchers from different disciplines (biology, chemistry, bioinformatics, physics and mathematics), as well as more advanced university students (from the bioinformatics curriculum the interdisciplinary curriculum Frontiers of Life Science, and from pharmaceutical science curriculum) acting as tutors for practical activities and group projects. The workshop articulates over a full week (5 days), for a total of 30 hours and it is organized in half-day modules. The first 5 half-days are disciplinary developing the theme of the study of the origins of life and presenting the tools for the study of RNA molecules in a molecular dynamics simulation. One half-day consists of a molecular dynamics lab on RNA folding. 3 half-days are dedicated to group work on an assigned subject. One half-day is devoted to the presentation of the group work.

Each disciplinary module is composed of short 10-20 minute lectures, with the professor introducing and developing concepts, mixed with short practical activities, while the longer activities (on-line scientific games) are proposed to students at the end of the modules (biology and chemistry) in order to introduce the main ideas of the game and its relation to the workshop [3]. Students are then encouraged to continue playing in their free time. At the end of the disciplinary module of chemistry and physics a quiz is proposed to the students to promote further reflection and possibly independent investigations (available in Supplementary Material). In the first workshop, the quiz was given as homework, while lately it is integrated in the modules and is used as a basis for group discussions and debriefing. Students are divided in small groups to answer the questions of the quiz. Then, groups are paired to form larger groups where the answers are reviewed and discussed in case of disagreement. Finally, the whole class comes together and the answers are once more reviewed in the presence of the instructor who steps in to redirect the discussion in case of mistakes.

2.3. The message and learning objectives

The central theme of the workshop is evolution, from the standpoint of molecular biology, with the hypothesis of an RNA world and the later development of DNA and proteins. Students discover a very rich molecular world that goes well beyond the DNA double helix that they are used to consider

as the basis of life. They discover the existence of RNA molecules of complex architectures that can act as the cells machineries also in the absence of proteins.
The various disciplines interplay, contributing complementary building blocks, focusing in particular on the following:

Biology. Concepts needed to address the question of the origin of life: From organisms to cells to molecules, Definition of a living organism, Darwins natural selection, LUCA (Last Universal Common Ancestor) and the main constituents of eukaryotic and prokaryotic cells, Different types of biomolecules (nucleic acids, proteins, lipids) and their functions, The role of water, RNA world hypothesis.

Chemistry. *Structural properties of biomolecules*: From atoms to biomolecules, atomic structures and properties, Intermolecular forces, interactions and folding of Proteins and Nucleic acids .

Physics. Concepts needed to build a molecular model and a molecular dynamics simulation: From classical mechanics to molecular dynamics, Newtons equations of motion and trajectories, Building a molecular model force-field, The role of temperature.

Mathematics. Quantitative analysis of a force-field: How to sketch a function from calculus, Maxima and minima to find equilibrium points, Limits to understand long and short range behavior of intermolecular interactions.

Computer science. Basic programming concepts and use of a molecular dynamics software: How to provide instructions to a computer, Programming elements (variables, functions, loops), Example of simple programming languages (SCRATCH and Python), Visualization tools (VMD[4] and UnityMol [5]), Interactive simulations [6].

3. The Workshop in detail

In this section we are going to present each teaching sequence, highlighting the main concepts discussed in class together with the activities proposed to the students as independent or group work.

3.1. Monday morning: Biology

The goal of the Biology module is to convey to the students the understanding that the most important properties of living organisms are determined and can be explained by their molecular properties. The fact that the role of RNA cannot be captured by the central dogma is put forward. This observation allows to point to other properties of RNAs, that are related to their capability to fold in 3D. This property is both directly related to the RNA world hypothesis and the molecular structure preparing the students to understand the importance of the point of view of the other disciplines.

The basic concepts for biology are provided via a series of short videos [7] available to the students before the workshop. The session then starts with a reminder of the definition of life. Depending on the level of the students, they are either asked to build their own definition or are given one by the instructor. The students are then asked to consider a list of words and to decide whether they correspond to living organisms or not. The following list has been constructed over time: Bee, palm tree, bacteria, mitochondria, virus, lichen, fish, computer virus, 3D printer, prion, fire. Many of these examples do not raise questions, but others do. For example, the bee is often considered problematic because only the queen reproduces in some cases, leaving the others apparently off evolution. Lichen, being a symbiosis, might also be seen as an issue. These two cases force the reasoning to occur at the level of species, not individuals. Viruses are also frequently the matter of intense debates, reflecting the ones of the scientific literature. This case is used to prepare students to see the influence of the initial definition put forward, but also the need to change their point of view, which echoes the fact that latter they will have to consider RNA for its potential role in the RNA world not just protein production.

In order to identify the main biological molecules of interest for a minimal origin of life scenario, the students are asked to build a portrait of LUCA. They are advised to start from the observation of current living organisms and to look for their common points that might have been already present in LUCA. They usually easily arrive at a cell, surrounded by a lipid bilayer, with genetic material made of DNA and RNA, and proteins. The structure/function relationships of the molecules can be highlighted: e.g. the lipids are amphiphilic which allows them to form bilayers, which in turn allows them to separate cell interior and exterior. This property has important consequences for evolution by maintaining together DNA and proteins. The link between genotype and phenotype is also highlighted for RNA, which

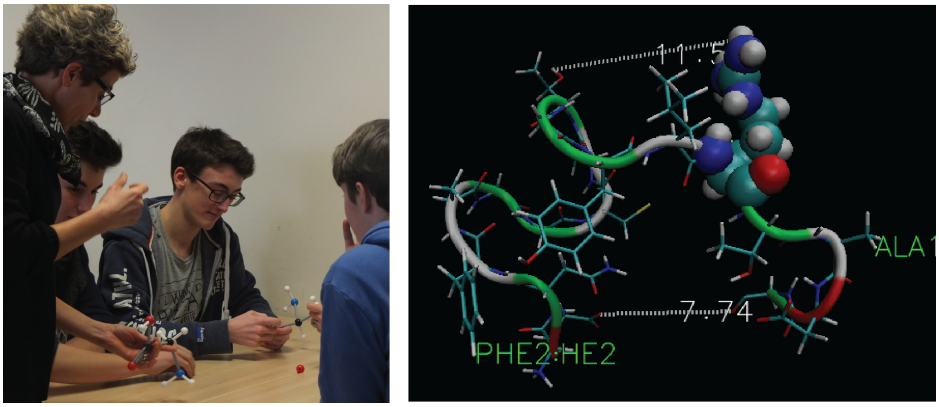

Figure 1: left: building amino acids using ball-and-stick chemistry kits, right: analysis of the same amino acids inside a peptide using the VMD software.

can both bear genetic information and act as a catalyst. It is underlined that both properties originate from RNA's ability to form hydrogen bonds, in replication and 3D folding.

The citizen science game Foldit [8] is used as a tool to allow students to experience the physico-chemical properties of proteins. The activity is inspired by the one described in ref [9].

3.2. Monday afternoon: Chemistry

The main goal of the chemistry module is to provide students with the understanding that in order to study the behavior of DNA, RNA and proteins it is necessary to look at the physical interactions that govern these systems. We start by briefly reviewing the structure of atoms, focusing on the geometries of the orbitals and electronegativity properties, highlighting how these two factors determine the kind of interactions forming between two atoms, ionic or covalent. For covalent bonds we focus on the relationship between the shape of the orbitals and the geometry of the molecules that are formed when these orbitals are involved in the bond. This part is given as a short lecture that includes several schematic videos [10]. Students are then asked to turn to a practical activity where they first have to build simple molecules (water, methane, ammonia) using chemistry ball-and-sticks kits. These same molecules are then studied in silico using the VMD software, where the students can make measurements of bond lengths and angles. We then resume the lecture and present the different kinds of non-bonded molecular interactions, namely the different electrostatic terms

(Coulomb and dipolar), Hydrogen bonds, and Van der Waals. These terms are presented in a qualitative fashion using movies and demos [10]. As practical activity, students are asked to use VMD to explore the structure of an ionic crystal, of liquid water and of ice.

The last part of the chemistry module is devoted to presenting proteins and nucleic acids and how they form structured molecules through folding. We first discuss the peptide bond that constitutes the backbone for proteins and look at the different physico-chemical properties of amino acid side chains discussing how their interactions lead the molecule from an unfolded, unstructured conformation to a well defined folded state. As a practical activity, students are asked to build two amino acids with the chemistry kit and to then form an oriented dipeptide. The dipeptide can then be visualized on VMD for a further, more quantitative analysis. On VMD the students can comparatively visualize the dipeptide as part of a full protein and start getting familiar with the fold of a protein as a whole (Fig. 1). At last, we introduce nucleic acids, focusing on the analysis of the interactions that nucleobases can form with each other. We discuss the double helix, but put the accent on how, based on the chemistry of the bases, it is possible to form many other base pairs that are non-canonical, and on how these pairs are often important in the 3D fold of single stranded RNA. Examples are provided with the help of several video materials [11, 12]. A group quiz is proposed before the longer practical activity.
We conclude the module with the on-line citizen science game EteRNA [13], where the students can explore the secondary structures of single stranded RNA molecules. In the game, students are asked to optimize an RNA sequence to obtain a given 2D structure. After guiding them through the first levels of the game, students are introduced to a module specifically addressing the hypothesis of an RNA world. In the latest workshop the activity has been replaced by Pangu, a game in augmented reality in which the player builds molecules with chemistry kits and take pictures of the molecules to make progress in the game [14].

3.3. Tuesday and Wednesday morning: Physics and Mathematics

The physics module focuses on explaining how to give a quantitative description of the molecular interactions described in the chemistry module. The goal is to show students that in order to study the interactions of molecules, they need to understand their physical behavior in terms of equations, and therefore they need to be familiar with some basic principles of

classical mechanics. In this module, we present the logical steps, and explain the main physical concepts, needed to build a molecular dynamics simulation: Newtonian dynamics, potential energies, and force fields. To present the concepts underpinning equations of motion, the relationship between potential energies and forces, as well as the concept of bound and unbound states, we recall some mathematical concepts from calculus, in particular limits and derivatives.

This module is at the heart of the workshop as it directly involves a discipline with which some students have difficulties. Here students have the chance to see first hand the role of physics and mathematics in the interdisciplinary challenges posed by the biological problem and understand their role in the overall picture. It is therefore important to focus on a few central concepts, to allow enough time to treat the subject, and to put at use different teaching tools. Thereby we always combine the formal presentation in terms of equations and mathematical analysis, with fun, practical exercises and hands-on examples to provide as much as possible the opportunity to build an intuition. The module is developed over two half-days, on Tuesday and Wednesday morning, with computer science done on Tuesday afternoon, to allow the students a break and focus on something more practical.

The module starts with a qualitative presentation of what molecular dynamics is, in order to clearly show that the goal of the module is to be able to understand the various steps of the simulation process. Having presented MD first allows to have a thread to follow to which the teacher can refer during the module to refocus the students on why the different physical concepts are needed.

The first concept presented is Newtons second law, F=ma, discussing what forces, accelerations, velocities and displacements are, and what an equation of motion is. At first, we give a discrete treatment in terms of finite variations of quantities over time. Next, we move to the continuum description using derivatives to define the velocity and the acceleration. We present the concept of derivative, highlighting its role as slope of a function, and review simple rules to compute such derivatives. The students work in groups to determine the equations of motion for a free-falling object. We then continue to present the principles of the harmonic oscillator, which will later be used extensively to model covalent bonds. An on-line exercise is proposed to explore the properties of this system and to visualize the behavior of the displacement as a function of time, from which students see first hand the arising of a sinusoidal function [15, 16]. To conclude this part, we discuss

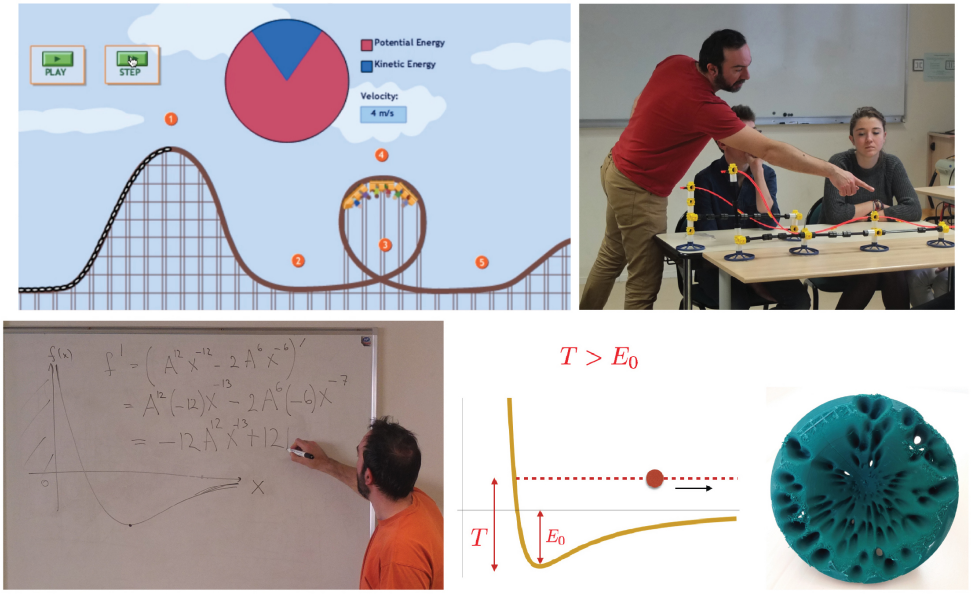

Figure 2: top left: energy conservation presented with the roller coaster applet, top right: marbles roller coaster to explain the concept of potential energy function, bottom left: the equation for an energy potential is discussed at the board, bottom center: the concept of binding energy and its relation to temperature is presented in a lecture, bottom right: 3D printed funnel (15cm diameter) to explore the role of temperature in finding the native state of a biomolecule.

Newtons third law of action and reaction to explain the behavior of multi-body systems and we review vector sums to combine multiple forces acting on the same particle.

The second chapter is devoted to energy: potential energy, kinetic energy and energy conservation. We first introduce potential energy and its relation to work and force. Marble roller coasters are used to familiarize students with the concept of potential energy function and equilibrium points. Together with the instructor, students build the equivalent of an harmonic potential function and of a Lennard-Jones potential and discuss the role of maxima, minima and long-range behavior. Next, we present kinetic energy, total energy and energy conservation in relation with the concepts of bound and unbound states based on the functional profile of the potential energy and the total energy provided to the system. Students further explore these

concepts through an online application with examples of a roller coaster and a skateboard [17].

The next section presents the functional forms commonly used to describe intermolecular potentials, that is harmonic functions for covalent bonds, inverse power laws for electrostatic interactions, Lennard-Jones for Van der Waals interactions. We review how to sketch the profile of a function computing the existence domain, limits and determining maxima and minima through derivatives. For each of the functional forms analyzed we discuss the possible existence of bound and unbound states based on the presence of minima and on the limits at large distances, and put this in relation with the molecular behavior we want to capture with these models (Fig. 2). Students are asked to do some calculations to sketch these potentials themselves.

The last section is devoted to the role of temperature from a microscopic point of view in relation to bound and unbound states and the depth of potential wells. We present the roughness of a biomolecular energy landscape and the role of temperature on the ability of the system to explore it. To make this concept clearer we ask students to shake a model of a roughed energy funnel printed in 3D with a small bead inside, representing a molecule exploring its energy landscape (fig. 2). To conclude the section, students are asked to explore the role of temperature on various forms of molecular interactions (charged particles, neutral particles,...) using online applets, guided by some questions [18, 19, 20].

The module concludes with a group quiz in which the students are asked to critically review the main physical concepts presented in the module in relation to their application to molecular modeling (see supporting material).

3.4. Tuesday afternoon: Computer science

Computer science is typically not a subject in the curriculum of first year life science students, however we considered it useful to introduce the basics of giving instructions to a computer, in order to provide students with some understanding of what a computer simulation is and to show them at least the existence of simple coding languages that can be used to perform data analysis. We approach the subject from a distance and first propose a practical activity seemingly unrelated to computers to make students understand the logic of giving instructions to a computer. Students are spread out in the room and each one is given a small Lego abstract construction of a dozen pieces of different shapes and colors. They are given 15 minutes to write down instructions on paper on how to build the exact object they

received, using only textual descriptions and no drawings. After that time they are asked to take a picture of the object with their phone and to disassemble it, leaving it on the table together with the instructions. Students swap places and in another 15 minutes they have to rebuild the object following the instructions. Reconstructed objects are then compared with the pictures of the originals. This activity is used to start a discussion session in which the successful and unsuccessful instruction strategies are analyzed and in which students are led to deduce what an effective way to give instruction to a machine would be. A short lecture is then given to describe the basic elements of a computer code: variables, loops and functions, presenting examples with the python programming language. The rest of the module is dedicated to practical activities, first using python and a series of exercises proposed by the code academy website [21], and then presenting an enzyme-docking code written using Scratch [22], a programing language developed by MIT to teach the basics of programming to children. After working on some common predefined exercises, students are instructed to choose one of the two programming languages and to either extend the enzyme-docking code to make it perform new functions, or to write a completely new code on a subject of their choice.

3.5. Wednesday afternoon: Molecular dynamics lab

One full half-day is dedicated to a computer lab where students use an interactive simulation software developed for our research activities [23, 24] to explore DNA double strand assembly and single stranded RNA folding. After the more abstract physics and chemistry modules, before the computer lab, we propose a physical activity in order to bring the students back to the central theme of the RNA world. In the human folding game, each student receives a T-shirt of different color, representing one of the RNA bases. The class is then asked to form chains of a given sequence and attempt forming contacts to reproduce given RNA secondary structure motifs such as double helix, hairpin and pseudoknots, as well as to optimize the sequence for a given structure, following up on what was done in the earlier EteRNA exercises.

After the game, lasting usually about 20 minutes, students start working at the computer lab using the UnityMol [25] software and entering the HiRE-RNA folding competition [26] (Fig. 3). The software performs a molecular dynamics simulation using a simplified, coarse-grained representation for nucleic acids, which is visualized in real time on the computer screen. By selecting a particle of the system it is possible to apply an external pulling

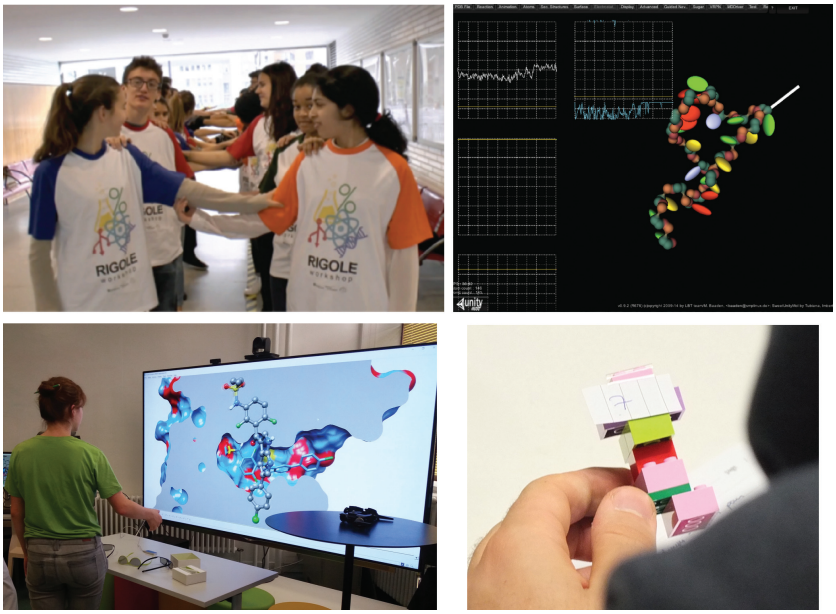

Figure 3: top left: human folding activity, top right: interactive RNA folding simulation on the computer, bottom left: interactive docking (for high school students in 2018), bottom right: example of lego structure used in the computer science module.

force, which is integrated in the Newtonian dynamics, allowing the user to pull the molecule toward a desired conformation. Pop-up graphs monitor different energy terms from which one can deduce for example when a base pair is formed. Students first familiarize with the software performing interactive simulations on the DNA double helix, then they have to solve four RNA folding puzzles with increasing complexity, from hairpins, to a pseudoknot, to a triple helix, starting from a completely unfolded configuration. By observing the stability of the conformations they generate and analyzing the graphs of the energy terms, the students select plausible native-like folded candidates and submit them to the HiRE-RNA folding contest web server to be automatically compared to the known experimental structures, receiving a score and a ranking in the class. As a side note, this student experiment brought up particularly interesting observations. We found that humans (e.g. students) explore phase space in a very different way compared to automated computational approaches, as discussed in more detail elsewhere [6].

In the 2018 workshop with junior high school students, a parallel session was added to the MD lab to present ligand-biomolecule interaction through

interactive simulations and virtual reality. This hands-on demonstration allowed to show yet another aspect of molecular modeling where the interplay between biology chemistry and physics is essential for conducting an *in silico* experiment addressing biomolecules.

3.6. Thursday and Friday morning: Posters group work and presentation

Students have 1.5 days to prepare a poster to be presented to the rest of the class on the last half day of the workshop. The poster session is the subject of a separate paper in preparation and will therefore not be described in detail here.

A number of pre-selected subjects ranging from more biological to more physical ones are proposed to groups of 3 or 4 students. Groups are chosen to be as much as possible heterogeneous and complementary in the disciplinary strengths of their members. Subjects include the role of clay in the formation of the first "cellular" compartments, Urey and Millers experiment for the creation of the first amino acids, the life cycles of phages comparing systems based only on RNA with those using also DNA, RNA thermometers, G-quadruplexes, ribozymes (Fig. 4). Students are encouraged to use the knowledge and tools explored in the disciplinary modules to address the subject from different angles. On purpose, we do not provide more than the title of each subject, to allow each group to develop its study creatively and critically. The poster presentation is organized as a rotation, so that each group member has the chance to present the work in front of a group of participants and a professor. For the workshops addressed to college students as a course, the poster session contributes to the students' grades. Through the rounds of presentations, each student is evaluated both by his peers and by a professor, and acts themselves as evaluator for other participants.

4. Goals Assessment

The workshop was offered so far to three high school groups of students, one of seniors and two of juniors, two 45-student groups from first and second year biology degree, and three 30-student groups from the first year of the interdisciplinary degree of "Frontiers of life science". To assess the impact of the workshop and its effectiveness with respect to the initial goals, we analyzed several factors which included a survey at the end of each workshop, results of the quizzes when these were given as homework, results of the folding challenge, quality of the posters produced in the group work, and the

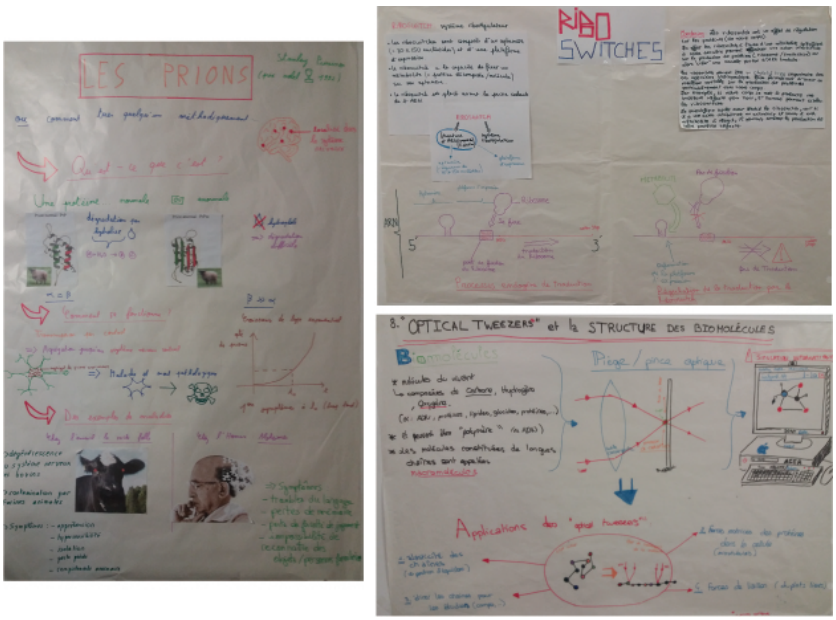

Figure 4: Examples of posters produced by high school juniors in 2018, spanning from more biological to more physical.

impressions of all instructors (eleven all together) on the students' attitude, participation, reflection... Even though the overall number of participants is not large enough to perform a statistical analysis of the impact of the workshop and given that some appreciations could only be qualitative, we nonetheless are able to draw some overall conclusions.

Students of all categories showed a great enthusiasm for the workshop. They very much appreciated the innovative teaching methods giving them a more active role than traditional teachings, as well as the learning environment in a more relaxed and fun setting. Their active participation grew over the days. While at first they were relatively shy, not being acquainted with a system where they were asked to participate in open discussions with professors and with classmates, they rapidly found their place building constructive interactions. This more direct relationship with the teachers opened the grounds for facilitated communication, essential to address the harder topics, thereby promoting a genuine and deep understanding of the subjects. The production of the students in the group work was satisfactory, with a good portion of posters reflecting the interdisciplinarity of the teachings of the week.

In the survey, students gave an excellent overall appreciation (100% good and very good), highlighted the overall coherence of the workshop (90% good and very good), noticing in their free comments how having a common thread through the various subjects helped them make connections and gave sense even to the more abstract concepts. They appreciated the coupling between more theoretical presentations and hands-on activities on the same topics (80% very good, 20% good), which they recognized helped them building an intuition. Despite the fact that some of the topics were of the same difficulty as those presented in regular courses, usually posing them problems, they did not find them too hard (60% medium difficulty, 20% slightly easy, 20% slightly hard). This appreciation was also reflected in the results of quizzes, with average scores significantly higher than those of similar tests given in disciplinary, traditional, courses taught by the same professors (12-13/20 for the workshop vs. 8-9/20 for quizzes in regular mathematics and physics courses).

College students answered that they believed having participated to the workshop would help them succeed in their studies (60%) and that they gained motivation toward scientific subjects (70%). Half of them answered that their attitude on how to learn science had changed. The large majority of high school students said that the workshop motivated them in the study of scientific subjects, changed their perspective on how to study science, and motivated them to pursue scientific studies in college. These answers for sure contained the bias of a student population already favorable to science from the start, but the high scores they gave to these appreciations were remarkable.

To further investigate the impact on high-school students, in 2018, we proposed a new, additional survey to gauge the initial interest of participants of the different subjects, their assessment of the importance of each subject to address biological problems, their perception about how easy or hard each subject is, and to what extent they would like to further study the subject in their future curriculum. The same questions were posed at the end of the workshop to see to what extent the program changed the students point of view. Questions and full results are available in supplementary material.

Students interest toward the four disciplines (biology, chemistry, physics and maths) was roughly equal at the beginning of the workshop. At the end of the workshop the interest for biology was increased significantly, while it remained steady for the other subjects. The initial perception of the difficulty

level of the four subjects ranked biology as a relatively easy subject, followed by the other three at medium difficulty. At the end of the workshop, biology was still considered the easiest, but to a lesser extent than previously thought. Chemistry, physics and maths were ranked medium/hard. The initial perception on the usefulness of the hard sciences in biology was that only chemistry was significantly useful, while all subject were useful for scientific research. At the end of the workshop all three hard science subject were considered essential for studies in biology. When asked if the workshop changed their perception on each subject, most students stated that their opinion did not change concerning maths, but that changed significantly for biology, chemistry and physics, and half of them stated that this brought them to re-evaluate their choice of future studies.
Overall, what emerges from this inquiry is that the workshop helped giving participants a more realistic perception of the four disciplines, and, as was our initial goal, helped them seeing the connections between them and the need for pursuing some knowledge of the hard sciences in order to make progress in biology. Interestingly, this seems to motivate students to pursue studies in biology even further than initially assessed.

Another criterion to assess the impact of the workshop was through the appreciations received by colleagues and institutions. The workshop has been an opportunity to spread innovative teaching methods among university professors. At first only three of the eleven teachers involved in the project were active users of unconventional teaching methods, and through the conception and the realization of the workshop the other teachers enthusiastically discovered the new methods and some of them applied them in other contexts as well. The workshop was presented in various teaching councils and faculty meetings, gathering significant interest also at the institutional level. As a consequence, after the first year when funding to cover all expenses, including teaching hours, was provided by an outside source (Idex USPC), the various disciplinary departments took charge of the teaching load allowing the workshop to continue to be offered both as a college course and as an extracurricular activity for high school students.

The workshop received also important institutional recognition being selected for the initial financial support by the "Paris Sorbonne Cité University" (USPC), and, more recently, from the joint Sao Paolo University - USPC grant to offer the workshop in Sao Paolo University in March of 2018.

5. Perspectives and conclusions

Convinced of the effectiveness of the teaching we have developed within this original workshop, in the three years since its first conception the workshop has evolved and parts of its content and teaching strategies have been used as blocks for other courses.

With the recent involvement of a Pharmacy department supporting the project, we have developed an alternative workshop based on the theme of the interactions of biomolecules with drugs. With respect to the original theme of the origins of life, this involves changes in the biology module, in the practical lab, and in the subjects given for the poster group work. Instead of folding an RNA molecule, in the new lab, students analyze the results of a molecular dynamics simulation of a protein interacting with a small ligand in its native sequence and structure and of a protein where mutations have been introduced near the ligand binding site. The subject of the posters are now focused on the binding of small ligands to proteins. For example, students are asked to investigate how caffeine and nicotine work at the molecular level. As further development, for the summer of 2018, an experimental wet lab will be introduced in which students will investigate the structure of biomolecules using biophysical techniques.

As an example of how the workshop can be easily be adapted to a different context, we illustrate our experience with a course for pharmacy students in an early elective research program, "pharmascience". The one-week setup of the workshop was proposed as biophysics/modeling course for students in their second year, adapting and changing certain modules to the higher level of these students and course requirements. The modules of chemistry and physics of RIGOLE were used as starting point to familiarize students with the structural analysis of biomolecules and modeling. For both subjects additional, more in depth, concepts were introduced. For example, for physics we devoted one half-day to normal mode analysis and related applications to proteins and nucleic acids. We developed more in depth the concepts from calculus on functional studies and asked students to perform comparisons of different functional forms to describe molecular interactions and to investigate the consequences of their possible choices. The computer lab on protein-ligand interactions was expanded to lead the students to make more quantitative observations and students were asked to write a short report. Instead of the poster group work, a paper on modeling DNA at different scales was chosen to be analyzed and presented by the students, with dif-

ferent groups being assigned a different scale (quantum description of bases interactions, atomistic description, coarse-grained description, mesoscale description).

A second example comes from the workshop offered in Brazil, addressed to master and Ph.D students in pharmaceutical science. The biology, chemistry and physics modules were preserved but adapted to the higher degree of experience of the students, as it was the case for pharmascience, but they were discussed in less time than for the RIGOLE workshop (two full days). The computer labs were expanded and a module on docking was introduced in addition to the analysis of molecular dynamics simulations on protein-ligand systems. The group work on drugs was maintained, but instead of posters, the groups had to prepare an oral presentation.

Taking a wider perspective, the concept, format and methods developed here can be easily exported to other scientific disciplines and subjects beyond the realm of biology/biochemistry. Indeed, the problems with traditional pedagogical methods which motivated us, and which we have outlined in the introduction, are common to the vast majority of the first year curricula in the hard sciences. The main key to developing similar workshops in other contexts is the choice of an appropriate subject: on the one hand, it should be specific enough to be introduced and explored satisfyingly in a short time frame without the need of too much pre-acquired knowledge; on the other hand, the subject chosen should lend itself to the investigation from different angles and methodologies, to promote the idea that science is not a compartmentalized endeavor and that each single aspect of a university curriculum contributes organically. Interesting examples of this kind can be found in all disciplines.

One example which is particularly well suited in the domain of the physical sciences is cosmology. In this context, an interdisciplinary workshop focused on the theory and observation of the basic features of the evolution of the Universe and its driving forces could be developed along similar lines as the one described in this article. The basic mathematical laws which describe the universe evolution are very simple to write down and understand even by first- or second-year undergraduates with no prior knowledge in the field. Furthermore, this subject involves many different physics sub-domains (astrophysics, nuclear physics, optics, fluid dynamics...), and features the interplay of phenomena governed by different characteristic scales (like it is the case for macromolecules). Also, computer simulations are an important tool in this subject, and one can easily envision the development of simpli-

fied toy-versions of the software which is used in real-life research. Finally, interactive on-line pedagogical tools centered on many different aspects of cosmology (Hubble expansion, cosmic microwave background, etc) are already available (e.g. [27, 28]) and can be integrated in the workshop.

In conclusion, our experience has shown us that offering an interdisciplinary approach to the study of biomolecular systems is effective at all levels of teachings, from high-school to graduate, especially when this teaching is carried out with a mixture of theoretical and practical activities. Given that many different subjects are addressed in the workshop from various disciplines, this combination of theory and activities becomes essential to lead the students to the understanding of all concepts. Offering a relaxed teaching environment, where fun activities are proposed, is interesting also for more advanced students. Indeed, proposing less academic activities forces them to think out of the schemes they are used to, helping them to acquire a more critical view even toward subjects they have previously studied in disciplinary courses.

We hope the present article will allow others to replicate and adapt the workshop in even more contexts.

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Initial survey
(results given in %)

1. My interest for the subjects proposed in the RIGOLE workshop is:

	none	weak	average	strong	exceptional
Biology	0	0	26	36	33
Chemistry	0	2	19	55	21
Physics	0	2	17	38	31
Maths	7	7	17	26	36

2. Evaluate the difficulty level of each subject:

	impossibly hard	really hard	hard	a bit hard	easy
Biology	0	7	14	40	33
Chemistry	0	5	17	48	21
Physics	0	10	26	43	27
Maths	5	10	29	36	21

3. Assess the importance of each subject for research (all fields):

	useless	a bit useful	useful	very useful	necessary
Biology	0	2	12	21	60
Chemistry	0	0	7	26	62
Physics	0	0	2	31	62
Maths	0	0	10	19	67

4. Assess the importance of each subject for research in biology:

	useless	a bit useful	useful	very useful	necessary
Chemistry	0	0	2	36	57
Physics	0	12	19	52	7
Maths	0	19	38	29	5

5. In the future I would like to deepen my knowledge of:

	not at all	a bit	some	a lot	absolutely
Biology	10	10	17	24	33
Chemistry	2	7	26	29	29
Physics	0	5	33	29	33
Maths	7	12	24	19	29

Final survey

1. My interest for the subjects proposed in the RIGOLE workshop is:

	none	weak	average	strong	exceptional
Biology	0	0	14	40	43
Chemistry	0	2	12	64	21
Physics	2	0	26	36	33
Maths	5	14	31	12	33

2. Evaluate the difficulty level of each subject:

	impossibly hard	really hard	hard	a bit hard	easy
Biology	2	5	31	45	14
Chemistry	2	10	31	43	12
Physics	7	12	36	40	2
Maths	5	12	29	38	14

3. Assess the importance of each subject for research (all fields):

	useless	a bit useful	useful	very useful	necessary
Biology	0	2	12	24	57
Chemistry	0	0	2	40	57
Physics	0	0	0	33	64
Maths	0	0	10	29	60

4. Assess the importance of each subject for research in biology:

	useless	a bit useful	useful	very useful	necessary
Chemistry	0	0	0	24	74
Physics	0	0	14	45	38
Maths	0	10	29	19	21

5. In the future I would like to deepen my knowledge of:

	not at all	a bit	some	a lot	absolutely
Biology	7	12	14	19	43
Chemistry	0	12	17	36	26
Physics	5	5	14	40	31
Maths	7	14	24	19	31

6. The workshop changed my view of:

	not at all	a bit	some	a lot	completely
Biology	17	24	26	19	12
Chemistry	14	21	29	24	10
Physics	17	31	21	27	12
Maths	31	19	19	2	2

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Modeling questions (True/False)

1. In a molecular dynamic simulation:
   a) Temperature has no importance.
   b) The higher the temperature the more the system goes toward the local minima.
   c) Temperature is always fixed at 300K.
   d) The higher the temperature the more the system explores different conformations.

2. In a molecular dynamic simulation, interactions between atoms:
   a) Are computed on the basis of quantum mechanics and derive from first principles.
   b) Are computed through effective potentials that try to reproduce some molecular properties.
   c) Are established universally and they are the same for all systems.
   d) Include nuclear interaction.

3. In a molecular dynamic simulation, particles interactions:
   a) Are always repulsive.
   b) Are always attractive, but thanks to the temperature they can escape this attraction.
   c) Always include a repulsive component representing the effect of the volume occupied by the particle.
   d) Can change during the course of the simulation.

4. In a molecular dynamic simulation:
   a) Newton's second equation F=ma is used to compute particles trajectories due to interaction potentials.
   b) Particles velocities are proportional to the force acting on them.
   c) Positions and velocities are obtained from integration of acceleration.
   d) There is only one force acting on any given particle.

5. In a molecular dynamic simulation, bonded interactions represent:
   a) Electrostatic interactions between neighboring particles.
   b) Hydrogen bonds, setting an equilibrium distance and the bond geometry through angles and torsions.
   c) The interaction between atoms nuclei.
   d) Covalent bonds, setting an equilibrium distance and the bond geometry through angles and torsions.

Physics questions (True/False)

1. The interaction between two atoms depend only on their distance and it is described by a potential of the form:

$$U(d) = U_0 \left(\frac{a^3}{d^3} - \frac{a^2}{d^2} \right)$$

where *d* is the distance.
What is the equilibrium distance of the two atoms is U_0 = 1eV and *a* = 0.2nm?

2. An object is suspended by a spring in a gravitational field:
   a) The amplitude of the oscillations increases.
   b) The frequency of the oscillations increases.
   c) The equilibrium position shifts upward.
   d) The equilibrium position shifts downward.

3. Two particles are charged +2e and -e respectively:
   a) The two particles can be placed in an equilibrium position.
   b) The two particles can form an ionic bond.
   c) The two particles can form a hydrogen bond.
   d) The most important interaction is the dipole interaction.

4. If, at a given time t, the total force acting on every particle of the system is zero:
   a) The conformation adopted by the system will remain the same all following times.
   b) If the velocity of each particle is zero at time t, it will remain zero at all following times.
   c) The system is at equilibrium.
   d) The energy of the system is zero.

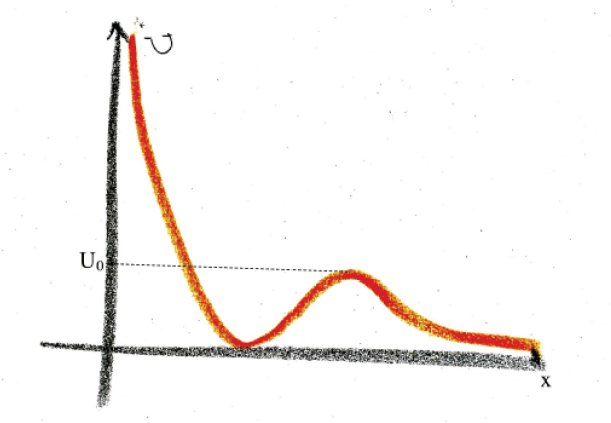
5. In a dissipative system:
   a) The total energy of the system and its environment is not conserved.
   b) The number of particles is not conserved.
   c) The system looses energy through heat.
   d) The system will end up in it global energy minimum.

6. Two molecules interact through a harmonic potential whose equilibrium distance is equal to *a*.
   a) If the temperature increases the frequency of oscillations around the equilibrium position increases as well.
   b) If temperature increases the amplitude of the oscillations around the equilibrium position increases as well.
   c) It is possible to break the interaction by raising the temperature.
   d) If the temperature decreases the molecules come into closer contact.

7. If a system of harmonic oscillators is at temperature T,

a) The average kinetic energy and the potential energy are proportional to T.
b) The average potential energy is equal to zero.
c) If the energy is sufficiently high the particles become free.
d) The average global energy of the system decreases with time.

8. The following diagram represents the potential energy *U* between two molecules as a function of their distance *x*.



a) The molecules can't be bound.
b) The molecules can't be separated.
c) The molecules are bound if their total energy is less than U_0.
d) The molecules are not bound if their total energy is greater than U_0.

Chemistry questions (True/False)

1. The spatial arrangement of a biopolymer is a consequence of:
   a) the equilibrium between the local interactions of the backbone and the electrostatic interactions of the backbone.
   b) its secondary structures.
   c) the equilibrium between covalent interactions, electrostatic interactions and interactions with the solvent.
   d) the shape of the atomic orbitals of the atoms composing the molecule.

2. The shape of a small molecule is a consequence of:
   a) the shape of the most internal orbitals of the atoms composing the molecule.
   b) the shape of the valence orbitals of the atoms composing the molecule.
   c) the equilibrium between the repulsion of nuclei and the attraction of the electrons with the nuclei.
   d) the electronegativity of the atoms composing the molecule.

3. The interactions characteristic of biomolecules giving rise to secondary structures in proteins and nucleic acids are:
   a) Hydrophobic interactions.
   b) Van der Waals forces.
   c) Coulomb electrostatic interactions.
   d) Hydrogen bonds.

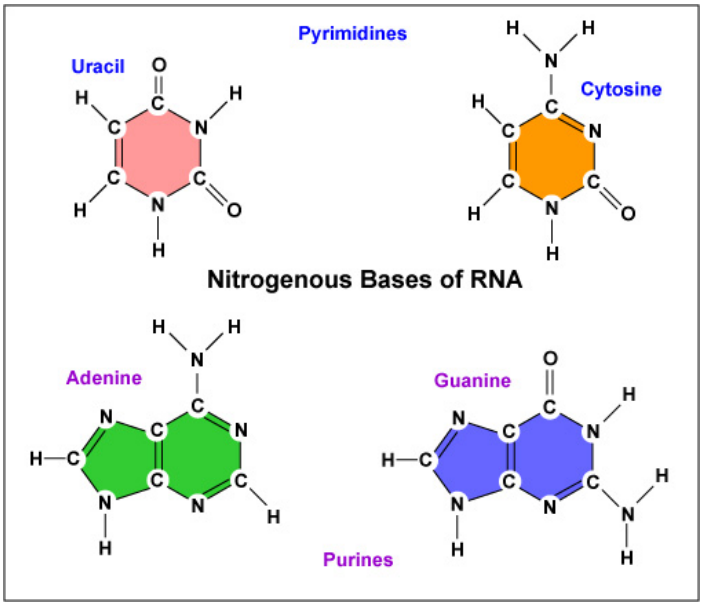
4. Because of the interactions with the solvent, a protein with many hydrophobic residues, in the water will have the tendency to:
   a) Fold in a globular shape.
   b) Remain unfolded.
   c) Form many hydrogen bonds.
   d) Adopt an elongated shape.

5. A single stranded RNA:
   a) Always folds in a double helix.
   b) Remains unfolded because it can't have perfectly complementary bases.
   c) Folds to form structures minimizing the interaction energies between its constituents.
   d) Can form complex structures that depend on the specific sequence and that can involve non-canonical pairings.

6. An RNA molecule is placed in a solution rich in positives ions.
   a) The strongest interactions (dominant) between portions of the molecule far way from each other are dipolar interactions.
   b) Molecules will be surrounded by an ionic cloud of positives ions to neutralize the negative charge of the phosphate groups.
   c) Coulomb's electrostatic interaction will be stronger at long distances because it will be amplified by the presence of the ions in solution.

d) The molecule will be surrounded by an ionic cloud of positives ions to neutralize the negative charge of the bases.

7. Looking at the chemical structure of the RNA bases, we can assert that:



a) There is only one possibility for base pairing: G with C and A with U.
b) Bases can all pair with one another, two at the time.
c) Bases can all pair with one another with the possibility for a base to be paired with two others.
d) There are multiple base pairings possible, but they always involve a purine paired with a pyrimidine.

8. X-ray crystals of nucleic acids always reveal the presence of Mg++ ions near the molecule. This explains because:

a) The ions form dipolar interactions with the molecule.
b) The ions form hydrogen bonds with the molecule.
c) The ions interact with the bases, which are negatively charged in solution.
d) The ions interact with the oxygen atoms of the phosphate groups, which are negatively charged in solution.

9. If a DNA helix is placed in a heat bath, as we raise the temperature the following phenomena are observed.

a) Base pairs break and the helix opens.
b) Molecular vibrations intensify.
c) The backbone of the molecule breaks.

What is the order in which these three phenomena occur as the temperature is raised?

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